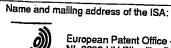
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From the INTERNATIONAL SEARCHING AUTHORITY To: WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43b/s.1) Date of mailing (dayshorathylear) see form PCT/SA220 (second sheet) Applicant's or agent's file reference See form PCT/SA220 FOR FURTHER ACTION See paragraph 2 below International application No. International filing date (dayshorathylear) Priority date (dayshorathylear) PCT/GB2004.001701 19.04.2004 Priority date (dayshorathylear) Priority date (dayshorathylear) 17.04.2003 International Patient Classification (IPC) or both national classification and IPC GOI N3368 Box No. II Priority Box No. II Priority Box No. II Non-establishment of opinion with regard to novelty, inventive step and industrial applicability Lack of unity of invention Box No. Vi Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement Box No. VI Certain documents cited Box No. VII Certain descriptions on the international application Box No. VII Certain descriptions on the international application Box No. VII Certain descriptions on the international application FURTHER ACTION If a domand for international preliminary examination is made, this coming with regard to considered to be a written opinion of the International Preliminary Examining Authority (PIPEA*). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the international Bureau under Rule 66.16/set) that written opinions of this international, before the expiration of thee months from the priority date, whichever expires later.	PATENT COOPERATION TREATY						
See form PCT/ISA/220 WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43b/s.1) Date of mailing (day/month/year) see form PCT/ISA/210 (second sheet) Applicant's or agent's file reference See form PCT/ISA/220 International application No. PCT/ISA/220 International pplication No. Prority date (day/month/year) 19.04.2004 International Patent Classification (IPC) or both national classification and IPC G01N33/68 Applicant UNIVERSITY COLLEGE LONDON 1. This opinion contains indications relating to the following items: Box No. I Basis of the opinion Box No. IV Lack of unity of invention Box No. IV Lack of unity of invention Box No. V Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, inventive step and industrial applicability citations and explanations supporting such statement Box No. VI Certain documents cited Box No. VII Certain documents cited Box No. VIII Certain defects in the international application Box No. VIII Certain defects in the international application Box No. VIII Certain defects in the international application Box No. VIII Certain defects in the international application Box No. VIII Certain defects in the international application Box No. VIII Certain defects in the international application Box No. VIII Certain defects in the international preliminary examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the international Bureau under Rule 68. Ibis(b) that written opinions of this International Searching Authority will not be so considered. If this continual Bureau under Rule 68. Ibis(b) that written opinion of the IPEA, the applicant in invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the deale of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.	INTERPASSED AND AND AND AND AND AND AND AND AND AN	REC'D 2 2 JUL 2004					
INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1) Date of mailing (clay/month/year) see form PCT/SA210 (second sheet) Applicant's or agent's file reference see form PCT/SA220 International application No. PCT/GB20044001701 International papilication No. PCT/GB20044001701 International Patent Classification (IPC) or both national classification and IPC G01N33/68 Applicant UNIVERSITY COLLEGE LONDON 1. This opinion contains indications relating to the following items: Box No. I Basis of the opinion Box No. II Non-establishment of opinion with regard to novelty, inventive step and industrial applicability Box No. No. III Non-establishment of explaint on the property of	To:	PCT PCT					
Date of mailting (day/month/year) see form PCT/SA/210 (second sheet)	see form PCT/ISA/220	(PCT Rule 43bis.1)					
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See form PCT/ISA220 International application No. PCT/ISA220 International application No. PCT/ISA2004.001701 International filing date (day/month/year) 17.04.2003 17.04.2003 17.04.2003 International Patent Classification (IPC) or both national classification and IPC G01N33/68 Applicant UNIVERSITY COLLEGE LONDON 1. This opinion contains indications relating to the following items: Box No. I Basis of the opinion Box No. II Priority Box No. II Non-establishment of opinion with regard to novelty, inventive step and industrial applicability Box No. IV Lack of unity of invention Box No. V Reasoned statement under Rule 43/bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement Box No. VI Certain documents cited Box No. VII Certain defects in the international application Box No. VII Certain observations on the international application Box No. VII Certain observations on the international application If a demand for international Preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA as notified the international Bureau under Rule 66. 15/s(b) that written opinions of this International Searching Authority will not be so considered. If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of malling of Form PCT/ISAA220.	Applicant's or search file						
PCT/GB2004/001701	see form PCT/ISA/220	FOR FURTHER ACTION See paragraph 2 below					
Applicant UNIVERSITY COLLEGE LONDON 1. This opinion contains indications relating to the following items: Box No. Basls of the opinion	PCT/GB2004/001701 19.04.2004	17.04.2003					
UNIVERSITY COLLEGE LONDON 1. This opinion contains indications relating to the following items: Box No. Basis of the opinion	International Patent Classification (IPC) or both national classification G01N33/68	and IPC					
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Jenkins, G

Authorized Officer

Telephone No. +31 70 340-2608



Box No. I Basis of the opinion
and the opinion
 With regard to the language, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.
This opinion has been established on the basis of a translation from the original language into the following language, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
a. type of material:
a sequence listing
☐ table(s) related to the sequence listing
b. format of material:
☐ in written format
☐ in computer readable form
c. time of filing/furnishing:
☐ contained in the international application as filed.
filed together with the international application in computer readable form.
furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional appropriate, were furnished.
4. Additional comments:

Bo	ox No. II Priority
1. 🛛	The following document has not been furnished:
	copy of the earlier application whose priority has been claimed (Rule 43 <i>bis</i> .1 and 66.7(a)).
	translation of the earlier application whose priority has been claimed (Rule 43 <i>bis.</i> 1 and 66.7(b))
	Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.
2. 🗆	This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43 <i>bis</i> .1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
	itional observations, if necessary:



International application No. PCT/GB2004/001701

E	Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability					
O.	The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:					
	the entire international application,					
Ø						
be	because:					
	the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):					
×	_					
☒	no international search report has been established for the whole application or for said claims Nos.					
	the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:					
	the written form		has not been furnished			
	·		does not comply with the standard			
	the computer readable form		has not been furnished			
			does not comply with the standard			
	the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions					
	See separate sheet for further o	details	S			



International application No. PCT/GB2004/001701

Box No. V Reasoned statement under Rule 43*bls*.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Yes: Claims

8,10,11,18-25

No: Claims 2-7,9,16,17

Inventive step (IS)

Yes: Claims

No: Claims

2-11,16-25

Industrial applicability (IA)

Yes: Claims

2-11,16-25

No: Claims

2. Citations and explanations

see separate sheet

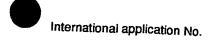
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Re Item III.

- 1 The following documents are referred to in this communication:
 - D1: ELLIS J ET AL: "Levels of dimethylarginines and cytokines in mild and severe preeclampsia." ACTA OBSTETRICIA ET GYNECOLOGICA SCANDINAVICA. JUL 2001, vol. 80, no. 7, July 2001 (2001-07), pages 602-608, XP002287424 ISSN: 0001-6349
 - D2: PETTERSSON ANDERS ET AL: "Increased circulating concentrations of asymmetric dimethyl arginine (ADMA), an endogenous inhibitor of nitric oxide synthesis, in preeclampsia" ACTA OBSTETRICIA ET GYNECOLOGICA SCANDINAVICA, vol. 77, no. 8, September 1998 (1998-09), pages 808-813, XP002287425 ISSN: 0001-6349
 - D3: DAYOUB H ET AL: "Lessons from a DDAH transgenic mouse: Role of ADMA in regulating NOS activity and blood pressure." EUROPEAN HEART JOURNAL, vol. 23, no. Abstract Supplement, 4 September 2002 (2002-09-04), page 132, XP008032589 & CONGRESS OF THE EUROPEAN SOCIETY OF CARDIOLOGY; BERLIN, GERMANY; AUGUST 31-SEPTEMBER 04, 2002 ISSN: 0195-668X
 - D4: US-A-5 811 416 (CHWALISZ KRISTOF ET AL) 22 September 1998 (1998-09-22)
 - D5: WO 2004/046314 A (UNIV LELAND STANFORD JUNIOR; LIN KEN YOUNG (US); COOKE JOHN (US)) 3 June 2004 (2004-06-03)
- Present claims 12 and 13 were not examined for novelty, inventive step or industrial applicability. They relate to the use of an ADMA antibody for the manufacture of means for diagnosis of pre-eclampsia. However, the application provides no technical support (Article 6 PCT) or disclosure (Article 5 PCT) for a specific ADMA antibody. Furthermore, such an antibody was not available at the time of filing. For example D5, which is published after the priority date of the present application, shows that detecting ADMA using an antibody required the development of a separate set of methods to modify SDMA and arginine such that SDMA and arginine would be readily distinguishable from ADMA.
- 3 The examination of claim 16 was restricted to the use of L-arginine for the manufacture of a medicament for inhibiting or preventing pre-eclampsia or inhibiting or preventing IUGR. This is because the application only provides

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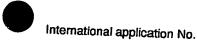
PCT/GB2004/001701

support (Article 6 PCT) and disclosure (Article 5 PCT) for L-arginine as an antagonist of ADMA activity (p. 10, lines 23-30 of the application).

Re Item V.

- 4 NOVELTY
- 4.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 2-7,9,16,17 is not new in the sense of Article 33(2) PCT.
- 4.1.1 D1 discloses (the references in parentheses applying to this document): plasma concentration of ADMA as a biomarker of pre-eclampsia in pregnant women at 24-32 weeks gestation, wherein controls range from 0.4-0.73 μmol/L and severe pre-eclampsia cases, 0.5-1.70 μmol/L (figure 1; discussion). Therefore, the subject-matter of claims 2-6,9 is not new in the sense of Article 33(2) PCT.
- 4.1.2 D2 discloses (the references in parentheses applying to this document): an increased ADMA/SDMA ratio as a biomarker of pre-eclampsia (p. 812, column 1, paragraph 2). Therefore, the subject-matter of claim 7 is not new in the sense of Article 33(2) PCT.
- 4.1.3 D4 discloses (the references in parentheses applying to this document): L-arginine for the treatment of pre-eclampsia (column 8, line 62 column 9, line 14). Therefore, the subject-matter of claims 16,17 is not new in the sense of Article 33(2) PCT.
- 5 INVENTIVE STEP
- 5.1 The present application does not meet the requirements of Article 33(1) PCT, because the subject-matter of claims 8,10,11,18-25 does not involve an inventive step in the sense of Article 33(3) PCT.
- 5.1.1 The subject-matter of claim 18 is not considered inventive under Article 33(3) PCT. Here, D3 is considered the closest prior art. This document discloses (the references in parentheses applying to this document): a transgenic

WRITTEN OPINION OF THE INTERNATIONAL EARCHING AUTHORITY (SEPARATE SHEET)



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mouse overexpressing DDAH, which results in reduced plasma ADMA levels. This causes an increase in NO synthase activity and a reduction in blood pressure, which is disclosed as being clinically relevant. Thus, D3 provides an animal model to study disorders characterised by changes in blood pressure and ADMA levels.

- In contrast, the subject-matter of claim 18 relates to an animal model of preeclampsia specifically, where the converse situation is present: ADMA levels are increased, rather than reduced, in order to cause a clinical effect.
- 5.1.3 The technical effect associated with this modification is that the mouse has pre-eclampsia.
- 5.1.4 The problem to be solved by the present invention may therefore be regarded as the provision of a mouse with pre-eclampsia.
- 5.1.5 The solution to this problem can be found in systemic administration of ADMA into a pregnant mouse.
- 5.1.6 The solution to the problem posed merely involves providing an obvious use for the "mirror image" of the animal model presented in D3. From D3, the person skilled in the art would automatically expect the converse situation to hold true: i.e. that increasing ADMA will bring about reduced NO synthase activity and increased blood pressure. Furthermore, there is an established link between pre-eclampsia and increased blood pressure (see abstracts of D1 and D2), where it has even been proposed that ADMA and the NO pathway are involved in the pathogenesis of pre-eclampsia (D2, p. 812, column 1, last paragraph). Thus, it would be obvious to produce an animal model of pre-eclampsia by increasing plasma ADMA levels in either normal mice or DDAH-deficient mice. Therefore, the subject-matter of claim 18, and also claims 19-25, does not involve an inventive step in the sense of Article 33(3) PCT.
- 5.2 The subject-matter of dependent claims 8,10,11 merely adds routine modification options to the subject-matter of claim 2 and is therefore obvious to a person skilled in the art. For this reason, the subject-matter of said claims does not involve an inventive step in the sense of Article 33(3) PCT either.

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- 6 INDUSTRIAL APPLICABILITY
- 6.1 The subject-matter of claims 2-11,16-25 is considered industrially applicable in the field of diagnosing and treating pre-eclampsia (Article 33(4) PCT).